PREVALENCE OF HIV INFECTION IN CHILDREN (0-12 YEARS) WITH TUBERCULOSIS AND CORRELATION OF CD_4 CELL COUNT LEVEL WITH TYPES OF TUBERCULOSIS

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CERTIFICATE

This is to certify that the dissertation titled "**PREVALENCE OF HIV INFECTION IN CHILDREN (0-12 YEARS) WITH TUBERCULOSIS AND CORRELATION OF CD_4 CELL COUNT LEVEL WITH TYPES OF TUBERCULOSIS "** is a original work done by **DR. T.SIVABALAN** in the Department of Pediatrics, Institute of Child Health and Hospital For Children, Egmore, Chennai – 600 008 and has been done under our guidance and supervision during the period of his post graduate study for M.D. (Branch VII) paediatrics.

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ABBREVIATIONS

TB -	Tuberculosis
PTB -	Pulmonary Tuberculosis
EPTB -	Extra Pulmonary Tuberculosis
LNTB -	Lymphnode Tuberculosis
DTB -	Disseminated Tuberculosis
TBM -	Tuberculous Meningitis
RNTCP -	Revised National Tuberculosis Control programme
BCG -	Bacillus Calmette Guerein
WHO -	World Health Organisation
NACO -	National AIDS Control Organisation
UNGASS -	United Nations General Assembly Special Session
IAP -	Indian Academy of Paediatrics
ICH & HC	Institute of Child Health and Hospital for Children
FNAC -	Fine Needle Aspiration Cytology
ARV -	Antiretroviral Drug
PMTCT -	Prevention of Mother to Child Transmission
$CD4^+$ -	$CD4^+$ T Lymphocyte
CCR5 -	Cytokine Cell Receptor 5
HIV -	Human Immuno deficiency Virus
AIDS -	Acquired Immuno Deficiency Syndrome

PCR - Polymerase Chain reaction

HAART - Highly Active Anti Retroviral Therapy

CDC - Centre for Disease Control

ELISA - Enzyme Linked Immunosorbent Assay

ALOC - Altered Level of Consciousness

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INTRODUCTION

INTRODUCTION

In Sanskrit, tuberculosis (TB) is known as “Rajyachhyama” or “the king of diseases”. It is one of the world’s most serious infectious threats. Tuberculosis is the second most common cause of death from infectious diseases at the global level, being second only to HIV/AIDS[1]. Tuberculosis in children is an important problem especially in countries like India where adult tuberculosis is common.

Globally it has been estimated that 1.9 billion people are infected with tuberculosis and 5000 people die of TB globally each day[1]. Tuberculosis probably causes 6% of all deaths world wide. One third of them are in Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan and Srilanka. The average prevalence of all forms of tuberculosis in India is estimated to be 5.05 per thousand and the average annual incidence of smear positive cases is 84 per 1,00,000 annually[1]. India has about 1.8 million new cases of tuberculosis annually, accounting for one fifth of new cases in the world, a greater number than any other country[1]. In 2004 about 3,30,000 people in India died from tuberculosis. Tuberculosis is one of the deadliest diseases in the world killing nearly 2 million people every year. More than 90% of all tuberculosis occurs in the developing countries.

According to the WHO, there where 4,50,000 deaths due to TB in children under 15 years of age in 1989. 75% of all childhood tuberculosis cases occur annually in 22 high burden countries mostly in sub-Saharan Africa. In developing countries, TB is responsible for 10% or more of the childhood hospital admission and 10% or more of hospital death. Recently the global burden of tuberculosis in children and its impact on child health are being increasingly recognized, in part because of the reemergence of tuberculosis as a major public health problem in developing countries.

Children less than 5 years old and infected with tuberculosis are at higher risk of developing disease probably due to immature cellular immunity. Exposure to tuberculosis is determined by the degree and nature of contacts with source cases as well as duration of infectiousness of the source cases. Factors such as family size, living space, population density, and the age of tuberculosis patients in a given setting determine the number of infections per infectious case.

Children can present with tuberculosis at any age but majority of cases present between 1 and 4 years. Disease usually develops within one year of infection in younger individuals and the progression to disease is earlier and more disseminated. Pulmonary tuberculosis is usually smear negative. Pulmonary tuberculosis (PTB) to extra

pulmonary tuberculosis (EPTB) ratio is usually around 3:1. In infants, the time span between infection and disease can be as little as 6 to 8 weeks[7].

Untreated adults pass the disease on to 43 % of children under one year and to 16 % of children from 11 to 15 years old. Only 5 to 10 % of adults with similar contact would contract the disease. Pulmonary tuberculosis is primarily an adult disease and it has been estimated that in 0 - 19 years old population pulmonary tuberculosis is only 7 %.

Childhood tuberculosis arises most often as a result of the inhalation of mycobacterium tuberculosis bacilli expectorated by sputum smear positive adult pulmonary tuberculosis patients through aerosol droplets. The infective aerosol droplets are 5-10 micrometer in diameter and contain 1-3 bacilli. If infection is successfully established, a primary focus form in the lung parenchyma, most often subpleural in location, and bacilli spread to regional lymphnodes and later via the lymph and blood to organs throughout the body. Depending upon the age and integrity of the immune system and perhaps the virulence of the infecting organisms, a majority of infections are either contained, usually at the site of primary focus and regional lymphnodes or may spread to extra pulmonary sites where the disseminated bacilli might get lodged.

TYPES OF TUBERCULOSIS

Pulmonary tuberculosis:

Primary tuberculosis denotes the first time infection in a previously uninfected child. The basic lesion formed during the primary infection, the primary focus (Ghon's focus), lymphangitis and lymphadenitis, are collectively called as primary complex of Rankey or pulmonary primary complex[19].

Progressive primary complex denotes the extension of the disease beyond the primary focus and the regional node by bronchogenic or hematogenous spread. The various forms of tuberculosis which develops following bronchogenic spread are as follows.

a) Incomplete bronchial obstruction with ball valve mechanism leading to obstructive emphysema.
b) Aspiration of caseous material into the lung may result in tuberculous bronchopneumonia and consolidation.
c) Complete obstruction with absorption of air results in collapse of the lung distal to the obstruction or collapse consolidation.
d) If these complications are not attended to, the sequelae is bronchiectasis

Secondary tuberculosis denotes all active tuberculosis which can occur any time after the primary infection or disease, due to endogenous

reactivation or exogenous reinfection. Other terminologies used are reinfection tuberculosis, post-primary tuberculosis, chronic tuberculosis or adult type of tuberculosis.

Hematogenous dissemination

Tubercle bacilli are liberated intermittently and gradually into the blood stream and carried to other parts of the body during the formation of primary complex. This can happen without the development of clinical illness resulting in disseminated lesion. If caseous node erodes a nearby vein and liberates large number of organisms, seeding may be sudden, heavy and widespread resulting in miliary tuberculosis[19].

Cavity formation is the hallmark of secondary tuberculosis, usually seen in the apices of the lung. Since the incidence of adult tuberculosis is high in our community, cavitating tuberculosis is increasingly seen even in younger age group. In adolescents fibrous bands, calcified spots in the pulmonary parenchyma, hilar nodes, mediastinal nodes and pleura indicate healed lesions.

Extrapulmonary tuberculosis

Children with extrapulmonary tuberculosis (EPTB) present with constitutional symptoms such as fever, loss of appetite, weight loss, malaise and fatigue. These patients manifest symptoms and signs related to the organ system involved. Since hematogenous spread of tuberculosis

is common in children, extra pulmonary complications are considerably high when compared to adults.

Tuberculous pleural effusion

It is due to seeding of pleura with Mycobacterium tuberculosis. It occurs due to lymphatic spread, 3 to 6 months after the initial infection. TB pleural effusion usually presents as an acute illness with fever, pleuritic chest pain, nonproductive cough and dyspnoea. Many children may present as silent effusion without much constitutional symptoms. The effusion is usually unilateral due to unexplained reasons but can be bilateral too[19]. Tuberculous effusion is straw colored and exudative in nature (protein concentration more than 3 g/dl). Empyema is a rare complication of untreated tuberculosis.

Pericardial involvement by TB may present as acute pericarditis, chronic pericarditis. Pericardial involvement results from direct extension of infection from adjacent mediastinal lymph nodes or through lympho-haematogenous route.

Tuberculous adenitis

Lymph node TB (LNTB) is the commonest form of EPTB. LNTB is considered to be the local manifestation of a systemic disease. Patients usually present with slowly enlarging lymph nodes and may otherwise be asymptomatic. Isolated cervical lymphadenopathy is most often seen in

about two-thirds of the patients who present with painless, matted, lymph nodes.

Gastrointestinal Tuberculosis :

Abdominal Tuberculosis can affect any part of GIT right from oesophagus. Ileum and ileocaecal region are commonly involved. Gastrointestinal TB can be of ulcerative, hypertrophic, ulcerohypertrophic, diffuse colitis and sclerotic forms. Abdominal pain is the most common symptom. Diarrhoea, anorexia, weight loss and fever are also common. Other symptoms include a moving lump in the abdomen, nausea, vomiting, malena and constipation[19]. A doughy feel of the abdomen, mass in the right iliac fossa due to hyperplastic caecal TB, lymph node enlargement and rolled up omentum may be clinically elicited. It can also present as intestinal obstruction or peritonitis.

Peritoneal Tuberculosis

Tuberculous peritonitis may present as acute abdomen or as chronic TB peritonitis which is of 3 varieties[19]:

a) Ascitic form

b) Encysted or loculated form

c) Fibrous form

Other abdominal sites

Hepatobiliary tract, pancreas and splenic TB

Bone and joint Tuberculosis

Skeletal TB is a haematogenous infection. It commonly affects the spine and hip joint. Other sites include knee, foot, elbow joints and hand bones. Rarely affects the shoulder joint.

Spinal TB is the most common form of skeletal TB. Constitutional symptoms generally occur before the symptoms related to the spine manifest. Lower thoracic and lumbar vertebrae are the most common sites of involvement followed by middle thoracic and cervical vertebrae. Usually, two contiguous vertebrae are involved but several vertebrae may be affected and skip lesions are also seen[19].

The infection begins in the cancellous area of the vertebral body, commonly in the epiphyseal location and less commonly in the central or anterior area of vertebral body. The infection spreads and destroys the epiphyseal cortex, the intervertebral disc and the adjacent vertebrae. It may spread to the neighbouring vertebrae[19]. The vertebral body becomes soft and gets compressed to produce either wedging or total collapse. The paravertebral abscess may compress the spinal cord or may track down to the mediastinum to enter around the trachea, oesophagus or into the pleural cavity. It may spread laterally around the sternomastoid muscle and form an abscess in the neck. Rarely, a thoracic cold abscess may

follow the intercostal nerve to appear anywhere along the course of nerve i.e. empyema necessitans.

Neurological Tuberculosis

Tuberculous meningitis

TB meningitis (TBM) accounts for 70%-80% of cases of neurological TB.

The disease usually evolves gradually over two to six weeks[19].

a) **The prodromal phase:** It lasts for two to three weeks and is characterized by a history of vague ill-health, apathy, irritability, anorexia and behavioural changes.

b) **Meningitic phase:** with the onset of meningitis, headache and vomiting become evident and fever develops. Focal neurological deficits and features of raised intracranial tension may precede signs of meningeal irritation. Focal or generalized seizures, cranial nerve palsies, complete or partial loss of vision are the major complications of TBM.

c) **Deep coma phase:** If untreated the terminal illness is characterized by deep coma and decerebrate or decorticate posturing. Without treatment, death usually occurs in five to eight weeks. Atypical presentations include acute meningitic syndrome simulating pyogenic meningitis, progressive dementia, status epilepticus,

psychosis, stroke syndrome, trigeminal neuralgia, infantile spasm and movement disorders.

Tuberculomas

Intracranial tuberculomas in patients under the age of 20 are usually infratentorial, but supratentorial lesions predominate in adults. Solitary tuberculomas are more frequent than multiple lesions. Tuberculoma is diagnosed by contrast enhanced CT scan as a ring enhancing lesion.

Ocular Tuberculosis

In ocular TB, the choroid is the most commonly affected structure. Primary ocular TB is extremely rare and it is usually secondary.

Disseminated / Miliary Tuberculosis

DTB refers to the involvement of two or more non-contiguous sites by TB disease. Dissemination can occur during primary infection or after reactivation of a latent focus/ reinfection.

Genito-urinary Tuberculosis

Genito-urinary tuberculosis is rare in the childhood as it occurs 5-6 years after the establishment of primary complex. Genito-urinary TB may present as dysuria, painless haematuria, flank pain, renal mass, sterile pyuria and recurrent urinary tract infection.

Perinatal tuberculosis:

Tuberculosis can be acquired in the perinatal period. Symptoms and signs are non specific. Diagnosis is by clinical suspicion, culture of gastric washings, liver biopsy specimens, lymphnode biopsy specimen, spinal fluid, ear discharge, endotracheal aspirate or bone marrow and perhaps x-ray. There can be two types of perinatal tuberculosis.

a) **Postnatal tuberculosis**:

Infections occur after birth via airborne inoculation from close contacts (family members or nursery personnel).

Clinical manifestation

The clinical presentation of tuberculosis is non-specific but is usually marked by multiple organ involvement. The neonate may look acutely or chronically ill. Fever, lethargy, respiratory distress, hepatosplenomegaly and failure to thrive may indicate tuberculosis in neonate with a history of exposure. About 50% of children borne to mothers with active pulmonary tuberculosis develop the disease during the first year of life if chemoprophylaxis and BCG vaccine are not given.

b) **congenital tuberculosis**:

Congenital tuberculosis is a very rare condition. Only 300 cases were reported in the literature till 1989. It is because placenta

forms a protective barrier against the invasion of the fetus by the tuberculosis bacilli.

Mode of infection:

Three possible modes of infection of the fetus have been proposed. Hematogenous infection via the umbilical vein transplacentally to the fetal liver, fetal aspiration of infected amniotic fluid and fetal ingestion of infected amniotic fluid[19].

Clinical manifestation:

The affected infant is frequently born premature, but signs of disease usually do not appear for several days or weeks. The most common presentation is with respiratory distress, lethargy, poor feeding, fever, irritability, abdominal distension and failure to thrive. Hepatosplenomegaly and lymphadenopathy are common.

Investigations:

Congenital tuberculosis is particularly difficult to diagnose and high index of suspicion is important when mothers have active tuberculosis and belong to low socioeconomic status. The mothers are often apparently healthy. Onset of progressive neonatal icterus with hepatosplenomegaly after two weeks of age and complication of severe pneumonitis with failure to thrive should arouse suspicion.

1) Mantoux test is frequently negative

2) Chest radiograph shows the presence of scattered infiltrates, bronchopneumonia, consolidation and computed tomography of abdomen may show periportal hypodensity.
3) Positive smear and / or culture results can often be obtained from gastric washings, liver biopsy, lymphnode biopsy, spinal fluid, ear discharge and endotracheal aspirate or bone marrow
4) Newer modalities like polymerase chain reaction (PCR) are highly beneficial in the diagnosis of congenital tuberculosis
5) Recently phage typing has been used to establish the identity of Mycobacteria isolated from mother and the infant.

Diagnostic criteria:

Diagnostic criteria for the diagnosis of congenital tuberculosis were laid down by Beitzki in 1935 and subsequently were revised by cantwell in 1994.

Diagnostic criteria for congenital tuberculosis – Revised criteria by cantwell

Proven tuberculosis lesions in the infant plus one of the following[5]

i) Lesion occurring in the first week of life

ii) A primary hepatic complex,

iii) Maternal genital tract or placental tuberculosis

iv) Exclusion of postnatal transmission by thorough investigation of contacts.

Prognosis:

The prognosis was poor in the pre-chemotherapy era, the reported survival rate was very low (around 50%), but since the advent of chemotherapy, the chance of successful treatment have improved the overall survival. Delay in the diagnosis contributes to the increased mortality[6].

Prevention:

Prevention should be possible through early detection of disease during pregnancy and institution of appropriate therapy. Routine neonatal BCG vaccination is indicated in developing countries.

HIV INFECTION IN CHILDREN:

EPIDEMIOLOGY AND TREND OF HIV IN INDIA:

Nearly 25 million people have died world over due to HIV since 1891. It is estimated that currently 38.6 million people live with HIV infection world over, of which 2.3 million i.e. 5.9% are children < 15 years of age. Though children represented only 6% of all these as of December 2005, they accounted for 18% of the 3.1 million AIDS deaths in 2005; and this is because only 40,000 or 4% of the one million people now on antiretroviral treatment are children. This means that one in every

six AIDS deaths each year is a child, yet children represent less than one of every twenty-five persons getting treatment in developing countries today.

In 2005, more than 540,000 children were born with HIV infection transmitted from their infected mothers, 90% of them in sub-Saharan Africa and remaining in Asia, mainly India.

The estimated total number of HIV infection in India was 3.5 million in the year 1998, 3.5 million in 1998, 3.71 million in 1999, 3.86 million in 2000, 3.97 million in 2001, 4.58 million in 2002, 5.1 million in 2003 and 5.134 million in 2004. The estimated number of children living with HIV / AIDS in India is 0.17 million (UNAIDS 2004 report) to 0.24 million (NACO estimates based on % of AIDS cases), which means that they form less than 3.5 – 5% of people living with HIV in the country[9].

Unlike in adults where more than 90% of the time HIV infection occurs through sexual route, in the developing countries 95% of cases in children occur due to vertical transmission from their infected parents. The risk of mother to child transmission of HIV infection varies from country to country and also within a country depending on the facilities available. It is 15-30% in non-breast feeding populations, whereas it is 30 – 45% in countries where breast feeding is a norm. This is because breast feeding has an additional 5- 20% risk of postpartum transmission[10].

In June 2001, the member countries pledged at the United Nations General Assembly Special Session on HIV / AIDS (UNGASS) to reduce the mother to children transmission of HIV by >20% by 2005 and by >50% by 2010. This was further reaffirmed at the United Nations summit in September 2005. However by 2005, only 9% of the pregnant women living with HIV infections actually received ARV prophylaxis for PMTCT world over.

TRANSMISSION AND PATHOGENESIS OF PAEDIATRIC HIV DISEASE

Transmission of HIV:

HIV virus is present virtually in all the body fluids of HIV infected individuals. Blood and genital fluids (seminal, vaginal and cervical secretions) contain high concentration of free HIV virus and HIV infected cells. Although saliva contains HIV (in very low titers < 1 infectious particles/ml), it is not likely a vehicle of transmission as it contains nonspecific inhibitory substances like fibroblasts and glycoproteins, which could prevent cell-to-cell transfer of virus. Urine, sweat, amniotic fluid, synovial fluid, faeces and tears have been reported to yield zero or a few virus particles. Hence, these vehicles also do not appear to be important in transmission[12]. The efficiency of HIV transmission is

determined by the amount of virus in the body fluid and the extent of contact.

Route of Transmission:

The usual routes of transmission in children are vertical transmission from infected mother to child; blood and blood product transfusions[18].

1. Vertical transmission from mother to child:

This is the primary route of infection in pediatric age group accounting for more than 90% of HIV-1 infected infants and children globally. Vertical transmission of HIV can occur during pregnancy (in utero) labour and delivery (intrapartum) or through breast-feeding (postpartum).

Rate of Transmission:

Without any intervention overall vertical transmission rates range from 16-20% in developed countries and 25-45% in developing countries[15]. This difference is largely attributed to prevalence of prematurity and under-nutrition among mothers in developing countries.

Timing and mechanism of transmission:

Virologic analysis of aborted fetuses indicates that HIV can be transmitted to the fetus as early as the first and second – trimester of pregnancy[17]. The highest percentage of transmission occur during labor and delivery, either through trans-placental transfer of virus (micro-

transfusion) during late pregnancy or at the time of labor and delivery due to exposure of the skin and mucous membrane to infected blood and cervico-vaginal secretions in birth canal. Infections through breast-feeding occur due to exposure of mucous membrane to free and cell associated virus in the breast milk. Some of the facts about transmission through breast-feeding are[18]:

1. Transmission can take place at any point during breast feeding.
2. About 70% transmission occurs during first 4-6 months.
3. The longer the breast-feeding is continued the higher is the risk.
4. Mixed feeding increases the risk of transmission (food antigen and pathogens traumatize the intestinal mucosa causing a breach in the integrity of epithelial layer thereby permitting the virus to enter the damaged mucosa).

Risk factors for vertical transmission:

Several maternal, viral and fetal factors influence the rate of vertical transmission. Prematurity, advanced maternal HIV disease, exposure to maternal blood, firstborn twin, rupture of membrane > 4 hour, breastfeeding and higher maternal viral load are associated with higher risks for HIV transmission. However, the relative contribution of each individual factor is yet to be determined. The reported transmission rate among women with plasma HIV RNA < 1,000 copies/mL is almost

0%[16]. However, transmission has been reported among women with all levels of maternal HIV RNA (including undetectable levels). Although caesarean section has shown to decrease the transmission rate, the additional rate, with the advent of availability of HAART, the additional benefit is probably negligible if the mother's viral load is <500 viral copies/ml.

2. Blood borne infections:

This is the most efficient route of transmission of HIV. HIV infected blood, blood products, transplanted organs or tissues and HIV contaminated improperly sterilized needles and syringes can transmit HIV[16]. Transmission through transfusion of infected blood or blood products account for 3-6% of pediatric infections. In recent years, mandatory screening of blood or blood products for HIV before transfusion has significantly reduced the risk of this mode of transmission; although a small number of cases still continue to occur in many developing countries.

Natural History and Pathogenesis of HIV-1 Disease in Children:

Three distinct patterns of pediatric HIV disease were described before the era of HAART viz. rapid progressors, slow progressors and long term survivors. Approximately 15-25% of HIV infected newborns are rapid progressors with appearance of symptoms during the first few

months of life and have detectable virus in the plasma in the first 48 hrs of life and a median survival of 6-9 months[17]. They are considered infected in utero. As the infections occur during the period of rapid expansion of CD4 cells in the fetus, the majority of the body's immunocompetent cells would be infected before their migration to the marrow, spleen and thymus. This results in efficient systemic delivery of HIV and establishment of infection before normal development of immune system causing more severe immune impairment. The viral load rapidly increases and peaks by 2-3 months of age and subsequently decline slowly. In contrast to the viral load in adults, the viral load in infants stays high for atleast the first 2 years of life.

Early HIV-1 replication in children has no apparent signs and symptoms. The incubation period of HIV-1 infection in children is generally shorter after perinatal infection compared to adult HIV-1 infection. B cell activation occurs in most children early in the infection[15].

Hypergammaglobulinemia with production of nonfunctional antibodies (polyclonal) is more common among HIV-1 infected children than adults, commonly noted as early as 3 to 6 months of age[18]. This response may reflect both dysregulation of T cell suppression and B cell antibody synthesis and active CD4 enhancement of B-Lymphocyte humoral response. There is a reduced ability to respond to new antigens

with appropriate immunoglobulin production. This results in greater frequency and severity of invasive bacterial infections in pediatric HIV-1 infection due to lack of prior antigen exposure. Depletion of CD4 lymphocytes may not be as readily apparent in HIV-1 infected infants and young children as they have relative lymphocytosis, including CD4 lymphocytes. However, the CD4 cell percentage is relatively similar at all ages in infants and children and can frequently be used to detect CD4 lymphocytes abnormalities caused by HIV-1 infection. In HIV-1 infected children, opportunistic infections are frequently more severe or rapidly progressing because these infections often represent primary infection as compared to reactivation infection commonly seen in adults.

Central nervous system (CNS) involvement is more common in pediatric patients than in adults. Macrophages, microglia and astrocytes play an important role in HIV neuropathogenesis. Infected monocyte (utilizing the cytokine cell receptor CCR5) may act as latent but inducible reservoirs of virus, and may carry virus to organs, particularly the brain in which they become resident. Although the specific mechanisms for encephalopathy in children are not yet clear, the developing brain with immature blood brain barrier and delayed myelinization in young infant is more vulnerable to invasion by HIV.

Clinical Manifestations:

HIV infection often presents with diarrhea, lymphadenopathy, hepatomegaly, splenomegaly, parotid swelling, Lymphoid Interstitial Pneumonitis.

Skin Manifestations:

The common skin infections seen in HIV infected children are seborrheic, atopic and generalized dermatitis, lesion due to nutritional deficiency, eczema, psoriasis, drug eruptions and alopecia.

Manifestations due to hematological abnormalities:

Anaemia presenting as pallor and thrombocytopenia, which can present with petechiae and ecchymoses is likely to be diagnosed as "immune thrombocytopenia"[2]

Cardiac Manifestations:

Cardiomegaly, congestive cardiac failure, non-bacterial thrombotic endocarditis, cardiomyopathy, pericardial effusion, cardiac tamponade, conduction disturbances and sudden death are known to occur[2]. Cardiomyopathy frequently accompanies HIV encephalopathy.

Gastrointestinal Manifestations:

Diarrhoea, dysphagia, retro-sternal pain, difficulty in drinking fluids and excessive salivation are related opportunistic infections.

Affection of Physical Growth:

HIV infection adversely affects the growth of infected children.

Neurological Manifestations:

HIV encephalopathy can present with developmental delay or with regression of milestones.

Malignancy:

Non-Hodgkin's lymphoma, leiomyomas, leukemias and leiomyosarcoma.

Nephropathy:

Proteinuria, hematuria, hypertension, renal tubular acidosis, acute renal failure and progression to end-stage renal disease.

Ocular Manifestations:

CMV retinitis, anterior uveitis, retinal detachment and vitreous hemorrhage are some of the ocular lesions observed in HIV infected children.

Opportunistic Infections:

Opportunistic infections constitute one of the commonest features of symptomatic HIV infection in children. In any immunodeficient disorder, the type of organisms predominantly encountered depends upon the type of immune defect[2]. HIV infection directly or indirectly affects the cellular as well as the humoral arms of the immune system. In

addition, associated factors such as malnutrition, use of immunosuppressive drugs and presence of indwelling catheters add to the defective immunity. Hence, these children suffer from viral, bacterial, fungal, protozoan as well as mycobacterial opportunistic infections.

Presumptive diagnosis of severe HIV disease in infants <18 months[2]:

Clinical criteria for presumptive diagnosis of severe HIV disease in infants and children less than 18months of age requiring ART in situations where virological testing is not available.

A presumptive diagnosis of severe HIV disease should be made if:

- The infant is confirmed HIV antibody positive; And
- Diagnosis of any AIDS-indicator condition(s) can be made; Or
- The infant is symptomatic with two or more of the following:

- Oral thrush;
- Severe pneumonia;
- Severe sepsis.

Other factors that support the diagnosis of severe HIV seropositive infant include:

Recent HIV- related maternal death; or advanced HIV disease in the mother;

CD4 < 20%.

Confirmation of the diagnosis of HIV infection should be sought as soon as possible.

Laboratory Diagnosis of HIV Infection[2]

<table>
<tr><th>Anti-HIV antibody tests</th><th>Antigen detection</th><th>Virus isolation / detection of viral nucleic acids</th></tr>
<tr><td>Screening tests (Micro well ELISA tests, Rapid tests)</td><td rowspan="2">P24 antigen assay</td><td>Viral culture</td></tr>
<tr><td>Supplemental tests (Western blot, line immunoassay, recombinant immunoblotting assay)</td><td>PCR tests (DNA / RNA)</td></tr>
</table>

Antibody Tests

For infants born to HIV positive mothers, the passively transmitted HIV antibodies persist in circulation till 18 months. Though antibody test at 12 months can be used to exclude the infection (if negative), it may be necessary to repeat the test at 18 months (especially if the test at 12 months is positive) to exclude maternally transmitted antibodies. The antibodies start waning off from 12 months of age in infants. In breast

feeding mothers, the test needs to be repeated 3 months after cessation of the breast feeding for excluding HIV infection in the child.

ELISA (Enzyme linked immunosorbent assay)

ELISA is the most common test used for detection of HIV antibodies (anti-HIV1 and anti-HIV2) and is almost 100% sensitive and specific. Various techniques include indirect ELISA, direct ELISA, competitive ELISA, antigen sandwich ELISA, and antigen-antibody capture assay.

Rapid Tests

The rapid tests yield results in up-to 3 to 30 minutes (as compared to ELISA which takes 3 hours), and have high sensitivity (100%) and specificity (99%). These include dot blot assays, particle agglutination (gelatin, RBC, latex, microbeads), HIV spot & Coomb's tests and fluorometric microparticle technology.

Western Blot Analysis

Western blot analysis is done by electrophoresis of plasma on pre-impregnated strip containing various antigens of HIV and is considered positive if at least 2 out of 3 bands (p24, gp41, gp120/160) are positive.

HIV p24 Antigen:

HIV p24 antigen can be detected and quantified using EIA, with high sensitivity (79%) and excellent specificity (99%) and correlates well with disease progression.

HIV Viral Culture:

HIV culture is a highly sensitive and specific test but requires high degree of expertise, high cost and intensive laboratory facilities. It helps in the early diagnosis of infection in newborns and is useful in infected patients who have not yet developed antibodies (window period, hypogammaglobulinemia, and late symptomatic phase with severe immunosuppression).

HIV PCR:

Two types of PCR are available; HIV-DNA PCR from provirus in infected T cells and HIV-RNA PCR from free virions in plasma. Quantitative PCR can detect as low as 10 copies/ml of virus in plasma. HIV PCR helps in early diagnosis in infected newborns and is useful in infected patients who have not yet developed antibodies.

HIV-DNA PCR

HIV-DNA PCR is a qualitative test that detects the proviral DNA integrated with the host cell, performed using the reverse transcriptase PCR.

HIV-RNA PCR

HIV-RNA PCR is a quantitative test using reverse transcriptase or nucleic acid sequence based amplification and branched chain DNA techniques.

CD4 Counts[2]:

Absolute CD4 counts and CD4 percentage are determined for deciding the level of immunosuppression, point of initiating antiretroviral therapy and monitoring the response to the therapy. CD4 cutoffs predict risk of clinical disease progression & mortality. CD4 percentage & CD4 counts are higher in infants compared to that of adults & fall to adult values by age 5 years. Also, the counts vary due to diurnal change, intercurrent illnesses, steroid treatment, splenectomy, etc. Hence repeated measurements are more informative than one single value. The absolute CD4 counts change with age of the child. CD4 percentage does not vary as much with age and hence this is used in determination of the level of immunosuppression. The decision to start antiretroviral therapy is based on clinical indicators supplemented with the CD4 counts. It also helps to monitor disease progression. When the CD4 count is more severely affected than the clinical stage, one should consider CD4 cutoff for initiation of antiretroviral therapy.

Tuberculosis in HIV:

Approximately 10 million people are estimated to be co infected with mycobacterium tuberculosis and HIV, and over 90% of these dually infected individuals reside in developing nations[1]. Worldwide, tuberculosis is the most common cause of death among patients with AIDS, killing one of every three patients[8].

People with latent tuberculosis are increasingly becoming florid with HIV, and many more are developing active tuberculosis because HIV is weakening their immune system. There are several important association between epidemics of HIV and tuberculosis

1) Tuberculosis is harder to diagnose in HIV positive people
2) Progresses faster in HIV infected people
3) In HIV positive people it is more likely to be fatal if or left untreated
4) Occurs earlier in the course of HIV infections than other opportunistic infections.
5) Is the only major AIDS related opportunistic infection that poses a risk of HIV negative people.

There is increased risk of tuberculosis among HIV infected children and infact coinfection with HIV occurs in upto 48% of the children with culture proven tuberculosis. Extra pulmonary and miliary

tuberculosis are more among younger children[6]. Children usually get tuberculosis from an infected close adult and disease in the children is usually a primary infection rather than reactivation disease. An asymptomatic child with a positive mantoux suggests a latent infection and all latent infections should be treated to prevent the disease. Drug resistant tuberculosis is on the rise and thus contact to drug resistant tuberculosis should be treated with assumption that any newly diagnosed infection is similarly drug resistant. If there is any patient with tuberculosis then all exposed family members should be screened for tuberculosis.

Clinical features

Pulmonary tuberculosis may present with nonspecific symptoms such as fever, weightloss, failure to thrive and cough. Features of presentation in HIV infected children are similar to those among non HIV infections.

Extrapulmonary Tuberculosis

Common sites involved are lymph nodes, disseminated TB, CNS TB, bone TB and TB of the serosal surfaces. With disease progression of HIV, atypical features of TB are more common[10].

Suspect TB if the child has:

a) Contact with adult who has pulmonary TB

b) Fever for more than 2 weeks

c) Chronic cough

d) Ongoing weight loss or poor weight gain

e) Pneumonia not responding to antibiotics

f) Recent glandular enlargement.

Mantoux test (tuberculin test)

It can be done from three months onwards. Induration more than 5mm is considered positive in HIV infected children. However negative result may be seen in over 50% of children with tuberculosis. Thus a negative result does not exclude TB.

Gastric lavage/ sputum examination:

Though acid fast stained sputum smears are positive in 50% to 70% of adults with pulmonary TB, children with TB disease rarely produce sputum voluntarily and have a low bacterial load. Three consecutive morning gastric aspirates have a better yield than a single sample. Better diagnostic yield is seen on culture.

Other fluids and tissues for culture:

Bronchoalveolar lavage, lung biopsy, lymphnode biopsy, serosal fluids and CSF may be used for diagnosis. Specimens should be cultured for 2 to 6 weeks by radiometric culture methods (Bactec) or culture on L-J medium for 8 weeks[12]. Antimycobacterial drug sensitivity should be

done on initial positive culture, if treatment fails or relapse occurs. If no organism is isolated from the specimen of the child, drug sensitivity test can be done on the isolate from the source case.

Chest X-ray:

May show

a) Localized pulmonary infiltrates with hilar adenopathy
b) Middle lobe collapse
c) Pleural effusion
d) In older children cavitatory tuberculosis.

Extrapulmonary cause:

Culture of affected body fluid or tissue obtained by fine needle aspiration or biopsy.

PCR assays:

Not useful as primary diagnostic tool because a negative PCR does not rule out TB and a positive result does not absolutely confirm M.tuberculosis infection. Also false positive rates are high with sensitivity ranging from 45-83%. Serological tests for TB are not very specific.

LITERATURE REVIEW

LITERATURE REVIEW

1. Frequency of HIV infection amongst children with disseminated tuberculosis and tuberculous meningitis in Aligarh (North India) – a low HIV prevalence area.

Done in Department of Paediatrics, Jawaharlal Nehru Medical College, AMU, Aligarh, India.

ABSTRACT

Objective:

To determine the frequency of HIV in children with disseminated tuberculosis and tuberculous meningitis in a low HIV prevalence area, and to study clinical profile of those found HIV positive.

Study design:

Cross-sectional, descriptive study.

Place and duration of study:

Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, India from February 2005 to January 2008.

Methodology

The study was conducted on 215 children under 14 years of age with either disseminated tuberculosis or tuberculous meningitis. HIV infection was diagnosed in accordance with WHO strategy II. In children

younger than 18 months, the strategy (to cut down costs) was to screen first by HIV antibody testing and subject only positive cases to virological tests. Parents of HIV positive children were also tested for HIV and counselled. The clinical profile of HIV positive patient was noted.

Results

The frequency of HIV in all cases of TB was 5.12%, while that in cases of disseminated tuberculosis was much higher (22%). No case with isolated tuberculous meningitis was HIV positive. The majority (45.45%) of patients with HIV were between 1-5 years of age. The mode of infection in 7 (63.63%) cases was parent to child transmission. Loss of weight, prolonged fever, pallor, hepato-splenomegaly and oral candidiasis were the commonest clinical manifestations among HIV positive patients.

Conclusion:

Clinically directed selective HIV screening in cases of disseminated tuberculosis can pickup undiagnosed cases of the same in areas with low prevalence of HIV infection.

2. HIV-1 co-infection in children hospitalized with tuberculosis in South Africa.

Done in Department of Paediatrics, University of the Witwatersrand, Johannesburg, South Africa. shabirm@mail.sailmr.wits.ac.za

ABSTRACT

Setting:

Hospitals associated with the Department of Paediatrics at the University of the Witwatersrand, Johannesburg, South Africa.

Objectives:

To define the prevalence of human immunodeficiency virus coinfection and differences in clinical presentation between HIV-infected and non-infected hospitalized children with tuberculosis.

Design:

Children were prospectively enrolled between August 1996 and January 1997.

Results:

Out of 161 children enrolled, 42% were HIV-infected, including 67/137 with pulmonary tuberculosis and 1/24 with extra-pulmonary disease. Positive microscopy or bacteriology did not differ by HIV status for children with either PTB or EPTB. Although age did not differ between HIV infected and non-infected children with PTB, non HIV

infected children with EPTB were significantly older than those with PTB (median age 32 months vs 14.5 months, p = 0.004). chronic weight loss, malnutrition and the absence of BCG scarring were more common in HIV infected children with PTB. HIV-infected children were also more likely to show cavitation (p = 0.001) and miliary TB (p= 0.01) on chest X-ray. Reactivity to tuberculin (> or = 5mm and > or = 10 mm in HIV infected and non-infected children, respectively) was significantly lower in HIV infected children, as were CD4+ lymphocyte levels. The mortality rate during the study was 13.4% in HIV infected children compared with 1.5% in non HIV infected children (p = 0.03).

Conclusion:

There is a high prevalence of HIV coinfection in children with TB. Progressive PTB and death are more common in HIV infected children. Tuberculin skin testing is of limited use in screening for TB in HIV infected children even when using a cut-point of > or = 5 mm.

3. Seroprevalence of HIV infection among pediatric tuberculosis patients in Agra,India: A hospital- based study - Summary

In this study which was carried over a period of 2 years, from 2003 to 2004, 270 paediatric patients with active Tuberculosis disease attending the OPD of S.N. Medical College, Agra were screened for Human Immunodeficiency Virus 1 and 2 antibodies. Of these, 23 were found to

be HIV-positive. Seroprevalence of HIV infection among paediatric TB patients in Agra is 8.51% (23/270). The HIV infection was found to be significantly higher, i.e. 82.61% in male children than in female children, i.e. 17.39%. Among the age groups, which were divided into 1, 2–5, 6–10 and 11–15 years, maximum cases of HIV-positivity, i.e. 65.22% was observed in the age group, 2–5 years of age. Among the HIV-positive children with TB, 86.75% were of pulmonary and 13.04% were of extra-pulmonary type. Among the vaccinated children, 65.22% were found to be HIV positive, while 34.78% of the HIV-positive children were not BCG vaccinated.

HIV positive children are more likely to suffer from prolonged fever, weight loss, failure to thrive, developmental delay, stunted growth, cough, anorexia, lethargy, lower respiratory tract infections and hepatosplenomegaly while HIV negative are more likely to suffer from fever, diarrhoea, lymphadenitis, pallor and LRTI. 82.60% (19/23) of these TB patients had a history of positive contact with HIV, i.e. one of the parents was HIV-infected. The mode of transmission of HIV infection among paediatric TB patients was perinatal as revealed during the counselling sessions (pre-test and post-test) of both the parents.

4. Jm Cohen et al studied UK based retrospective study from 1991-2006 about TB and HIV co-infection. They studied 328 children (<16 yrs of Age) with HIV. Retrospectively they found that 18 were co-infected with TB. Among the 18,10 were known HIV at the time of presentation. They concluded that screening of HIV in TB is the must.

5. Madhi SA et al studied the HIV Co-infection in children with tuberculosis at the Dept. of Paediatrics, University of Witwatersrand Johannesburg, South Africa. They prospectively enrolled 161 children (<15years) with tuberculosis between August 1996 to January 1997 out of that 42% of children were found to have HIV infection. So they concluded that high prevelance of HIV coinfection is seen with Tuberculosis

STUDY JUSTIFICATION

STUDY JUSTIFICATION

1. India has a high prevalence of HIV. However the prevalence of HIV in children who are newly diagnosed as TB is not known.
2. To the best of our knowledge there are no such studies in Tamilnadu.
3. TB statistics in our Institute of Child Health.

ICH & HC Statistics

Year	Total TB Cases Registered in TB Clinic
2003	679
2004	697
2005	791
2006	650
2007	458

In spite of large number of patients treated at ICH every year, there is no study about HIV screening in Tuberculosis infected children.

4. The diagnosis of HIV in a TB patient has got varied consequences over the outcome as well as the treatment schedule for the disease.

5. The other part of my study deals with possible relation between the level of immunosuppression in HIV and the type of tuberculosis in that child.
6. If there is a positive correlation, then proper guidelines regarding the same could be recommended.

AIM OF THE STUDY

AIM OF THE STUDY

To document the prevalence of HIV infection among children with tuberculosis and correlation of CD4 cell count level with types of tuberculosis.

MATERIALS AND METHODS

MATERIALS AND METHODS

STUDY DESIGN :

Descriptive study

PLACE:

Institute of Child health and hospital for Children, Egmore, Chennai.

PERIOD OF STUDY:

2 years (OCT 2008 to OCT 2010)

STUDY POPULATION:

Children 0 to 12 years.

INCLUSION CRITERIA

Children aged below 12 years who are registered in TB Clinic at ICH.

Children with parents who gave consent for the study.

EXCLUSION CRITERIA

Children with parents who did not give consent for the study.

Children who are known to be HIV positive already.

METHODOLOGY

All children who are diagnosed as Tuberculosis using the modified Kenneth Jones criteria are included in this study after getting the consent of their parents.

Modified Kenneth-Jones criteria for the diagnosis of TB in children[23].

Score +3	Score +2	Score +1	Score -1
Recovery of AFB from sputum, gastric aspirate, laryngeal swab, etc.	X-ray chest suggestive of para-hilar lymphadenopathy with or without parenchymal lesions	Non-specific chest X-ray changes	BCG vaccination in the last 2 years
Tuberculous granuloma, granulomatous lesions in lymph node biopsy or choroid tubercles on fundoscopy	Suggestive physical findings: pleurisy, skin lesion, osteomyelitis, Pott's spine etc.	Compatible physical findings: erythema nodosum, phlyctenular conjunctivitis, meningitis, cervical lymphadenitis, arthritis, hemoptysis, etc.	
Positive Mantoux test (MT) induration exceeding 10 mm	Doubtful MT (5-9mm)	History of contact With a patient suffering from TB	
	Recent MT conversion from negative to positive	Non-specific granuloma	
	Contact with sputum smear-positive patient	Age below 2 years	
		Non-response to therapy	
		3rd degree protein- energy malnutrition	

According to this scoring system, 7 or more points indicate unquestionable TB; 5-6 points indicate probable TB, therapy may be justified; 3-4 points indicate that further investigations are needed.

Types of Tuberculosis

1. Pulmonary Tuberculosis
2. Lymph node Tuberculosis
3. Abdominal Tuberculosis
4. Central Nervous System Tuberculosis (Tuberculoma / TBM)
5. Spine Tuberculosis

Those children for whom the parents have consented are subjected to tests like ELISA or PCR as per their age for the diagnosis of HIV . The WHO/NACO/UNAIDS strategies for diagnosis of HIV infection is followed. In our study, strategy 2 and 3 are used for the diagnosis of HIV.

STRATEGY	
STRATEGY 1	Serum is subjected to ELISA/simple and rapid antibody test once. If negative the serum is considered as free of infection
STRATEGY 2 (symptomatic individuals)	Sample is considerd negative if the first report is negative. If positive, is subjected to second ELISA antibody test and reported positive if the second test is positive.
STRATEGY 3 (Asymptomatic individuals)	Additional to strategy 2 this includes a third ELISA confirmation before reporting as HIV positive.

Those children who are HIV positive are subjected to further test. CD4 count is done for all children who turned out to be HIV positive at the ART centre and results are collected, extrapolated and analysed. The CD4 grading is done according to the WHO revised classification of immunosuppression in children.

Grading of immune status based on WHO Revised classification of immunosuppression in children[2].

Grade of Immunosuppression	CD4 values (%) <11 months	CD4 values (%) 12-35 months	CD4 values (%) 36-59 months	CD4 values (%) <5 yrs (cell/ mm3)
Not significant	>35	>30	>25	>500
Mild	30-35	25-30	20-25	350-499
Advanced	25-30	20-25	15-20	200-349
Severe	<25	<20	<15	<200 or <15%

ANALYSIS

The results are extrapolated and analysed for HIV positivity rate among the Tuberculosis children and a correlation between CD4 count and type of TB was looked for. Data analysis was done with use of SPSS, version 10.Descriptive statistics were used to calculate the frequency,

mean, median and standard deviation. To examine the linear trend of proportions, trend chi-square was used and to findout the test of association chi-square was computed.

ANALYSIS OF OBSERVATION

ANALYSIS OF OBSERVATION

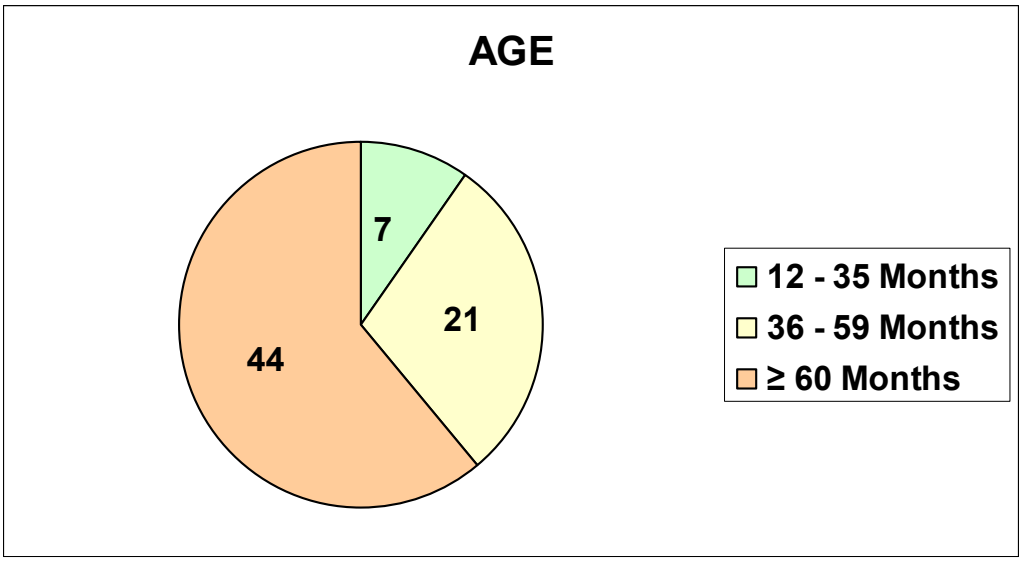
PREVALENCE:

TOTAL TB INFECTED CHILDREN	742
HIV CO INFECTION	72
PREVALENCE	9.7%

AGEWISE DISTRIBUTION OF TUBERCULOSIS

Age	Frequency	Percent
12-35 months	7	9.7
36-59 months	21	29.2
≥ 60 months	44	61.1
Total	**72**	**100**

AGEWISE FREQUENCY OF TUBERCULOSIS

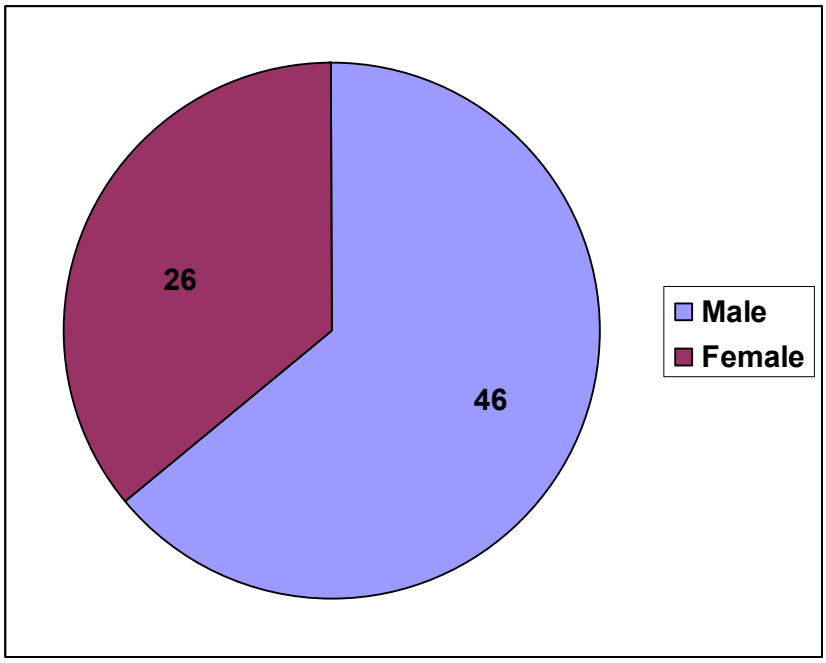


In our study the the maximum distribution was seen in age group of more than 60 months (61.1%).

SEXWISE DISTRIBUTION OF TUBERCULOSIS

Sex	Frequency	Percent
Male	46	63.9
Female	26	36.1
Total	**72**	**100**

SEXWISE FREQUENCY OF TUBERCULOSIS

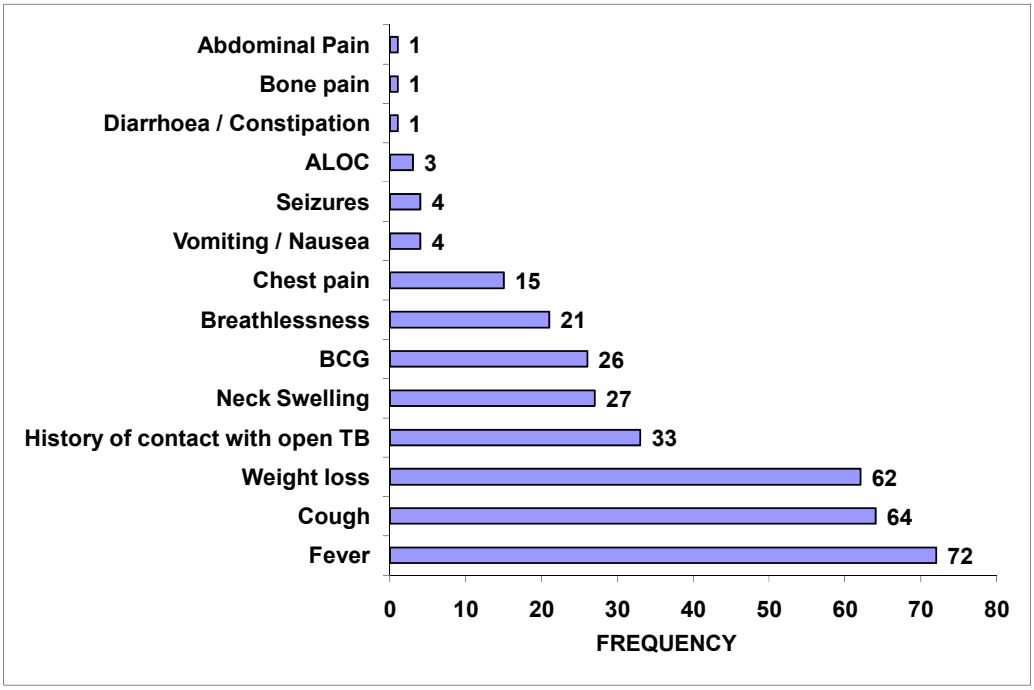


In our study the maximum distribution is among the male children (63.9%) than female children(36.1%)

CLINICAL MANIFESTATIONS

Clinical Features	Frequency			Percent		
	Yes	No	Total	Yes	No	Total
Fever	72	-	72	100	-	100
Cough	64	8	72	88.9	11.1	100
Weight loss	62	10	72	86.1	13.9	100
History of contact with open TB	33	39	72	45.8	54.2	100
Neck Swelling	27	45	72	37.5	62.5	100
BCG	26	46	72	36.1	63.9	100
Breathlessness	21	51	72	29.2	70.8	100
Chest pain	15	57	72	20.8	79.2	100
Vomiting / Nausea	4	68	72	5.6	94.4	100
Seizures	4	68	72	5.6	94.4	100
ALOC	3	69	72	4.2	95.8	100
Diarrhoea / Constipation	1	71	72	1.4	98.6	100
Bone pain	1	71	72	1.4	98.6	100
Abdominal Pain	1	72	72	1.4	98.6	100

FREQUENCY OF CLINICAL MANIFESTATIONS:

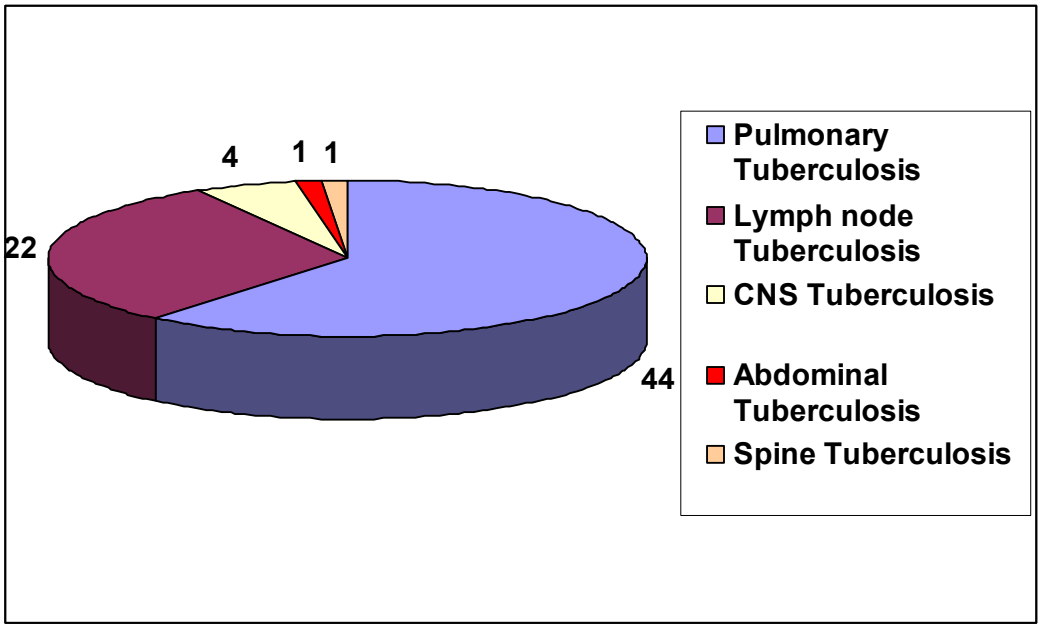


In our study the most common clinical manifestation is fever (100%) and the least common symptom was abdominal pain(1.4%).

TYPES OF TUBERCULOSIS IN CHILDREN COINFECTED WITH HIV

Types of TB	Frequency	Percent
Pulmonary Tuberculosis	44	61.1
Lymph node Tuberculosis	22	30.6
CNS Tuberculosis	4	5.6
Abdominal Tuberculosis	1	1.4
Spine Tuberculosis	1	1.4
Total	**72**	**100**

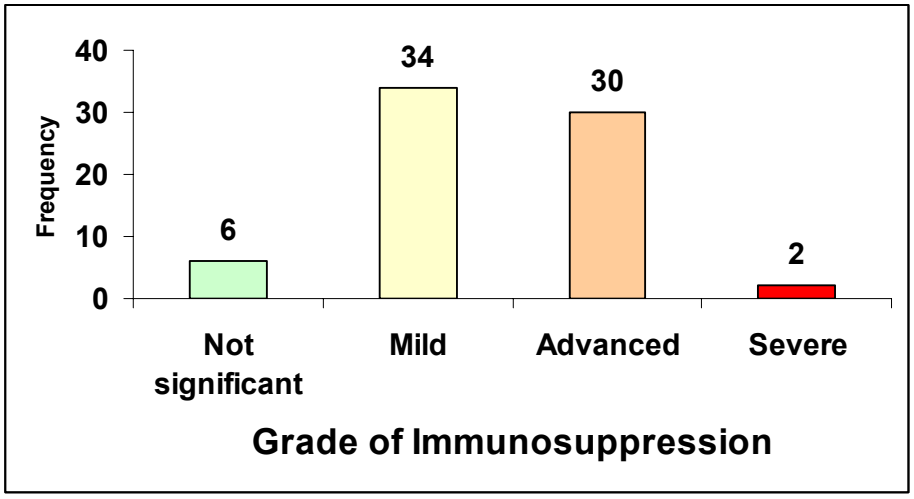
FREQUENCY OF TYPES OF TUBERCULOSIS WITH HIV COINFECTION



In our study the most common type of TB was pulmonary TB in HIV/TB coinfection.

CD4 COUNT LEVEL

Grade of Immunosuppression	Frequency	Percent
Not significant	6	8.3
Mild	34	47.2
Advanced	30	41.7
Severe	2	2.8
Total	**72**	**100**



In our study 41.7% of HIV-TB co infected children were in the advanced stage of immunosuppression.

TUBERCULOSIS TYPE & CD4 LEVEL CORRELATION

Types of Tuberculosis	CD4				Total
	Not significant	Mild	Advanced	Severe	
Pul TB No.	3	20	19	2	44
% of Total	6.8%	45.5%	43.2%	4.5%	100%
Lym TB No.	2	11	9		22
% of Total	9.1%	50%	40.9%		100%
CNS TB No.			1	3	4
% of Total			25%	75%	100%
Abd TB No.			1		1
% of Total			100%		100%
Spine TB No.				1	1
% of Total				100%	100%
Total	5	31	30	6	72
	6.9%	43%	42%	8.1%	100%

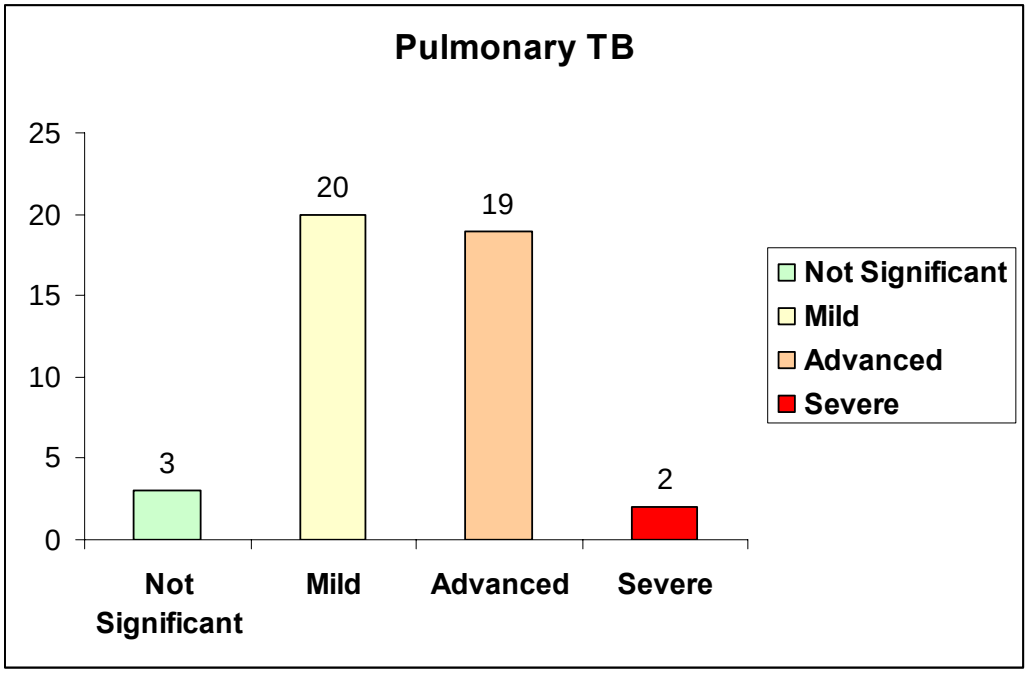
CD4 CORRELATION WITH TYPE OF TUBERCULOSIS

CD4 Count	Pulmonary TB	Lympnode TB	CNS TB	Abdominal TB	Spinal TB	Total
Not Significant	3 60%	2 40%	-	-	-	5 100%
Mild	20 64.5%	11 35.5%	-	-	-	31 100%
Advanced	19 63.3%	9 30%	1 3.3%	1 3.3%	-	30 100%
Severe	2 33.3%	-	3 50%	-	1 16.7%	6 100%
Total	44 61%	22 30%	4 5.5%	1 1.75%	1 1.75%	72 100%

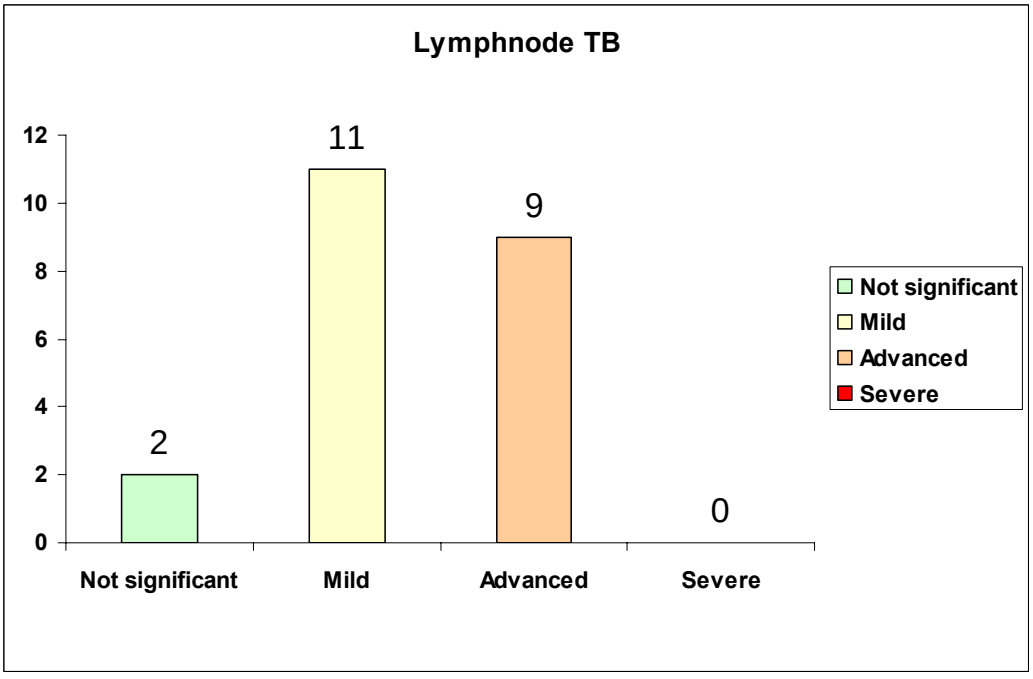
p value is 0.04.

In our study CNS, abdominal & spinal tuberculosis were seen only in advanced and severe grade of immuno suppression.

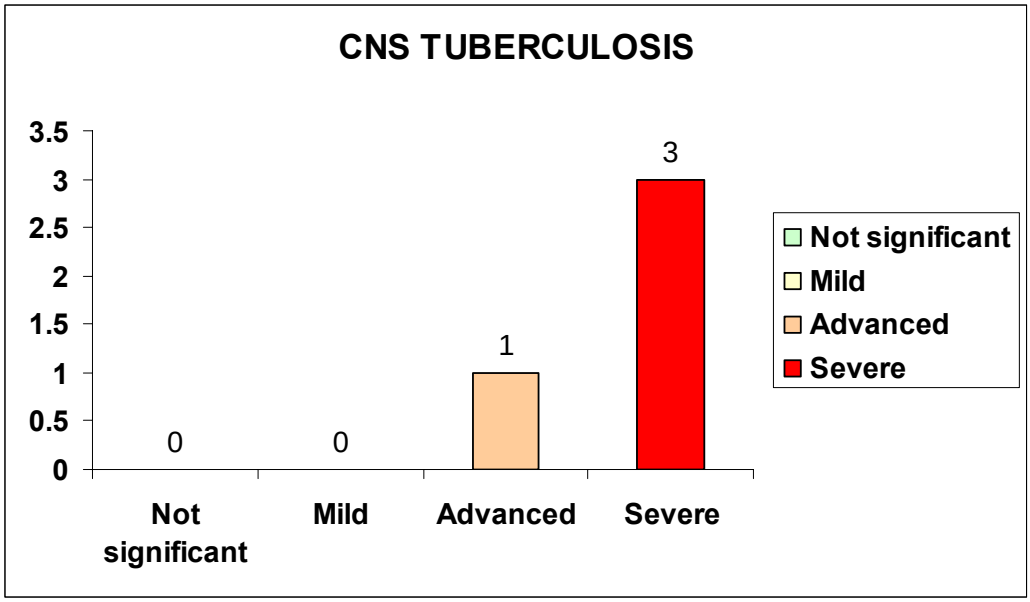
DISTRIBUTION OF PULMONARY TB IN RELATION TO IMMUNOSUPPRESSION



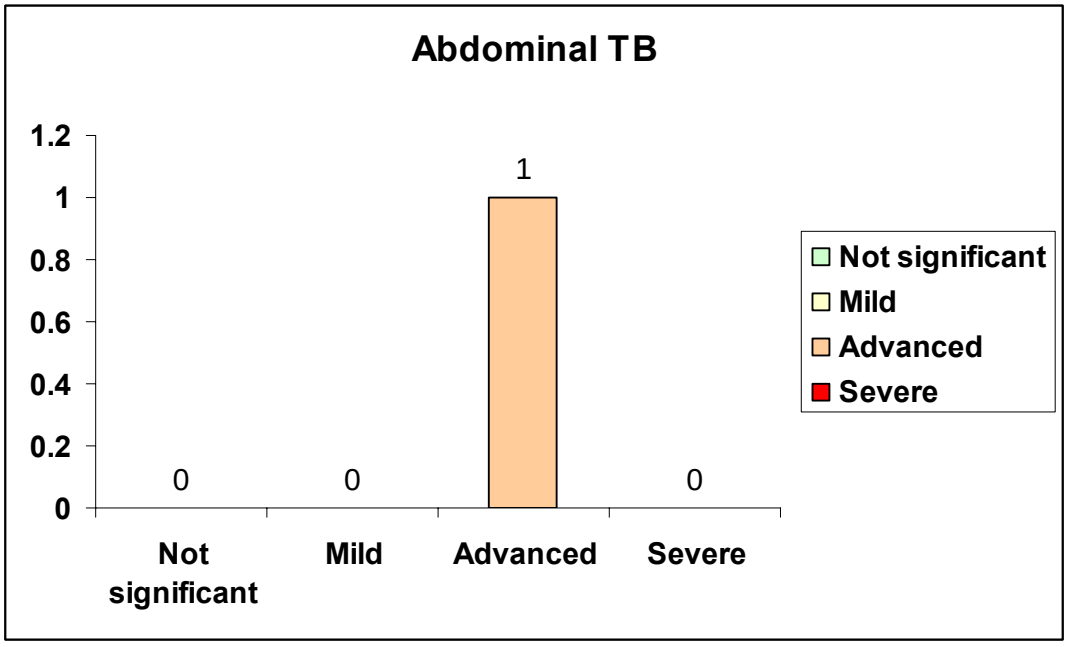
DISTRIBUTION OF LYMPHNODE TB IN RELATION TO IMMUNOSUPPRESSION



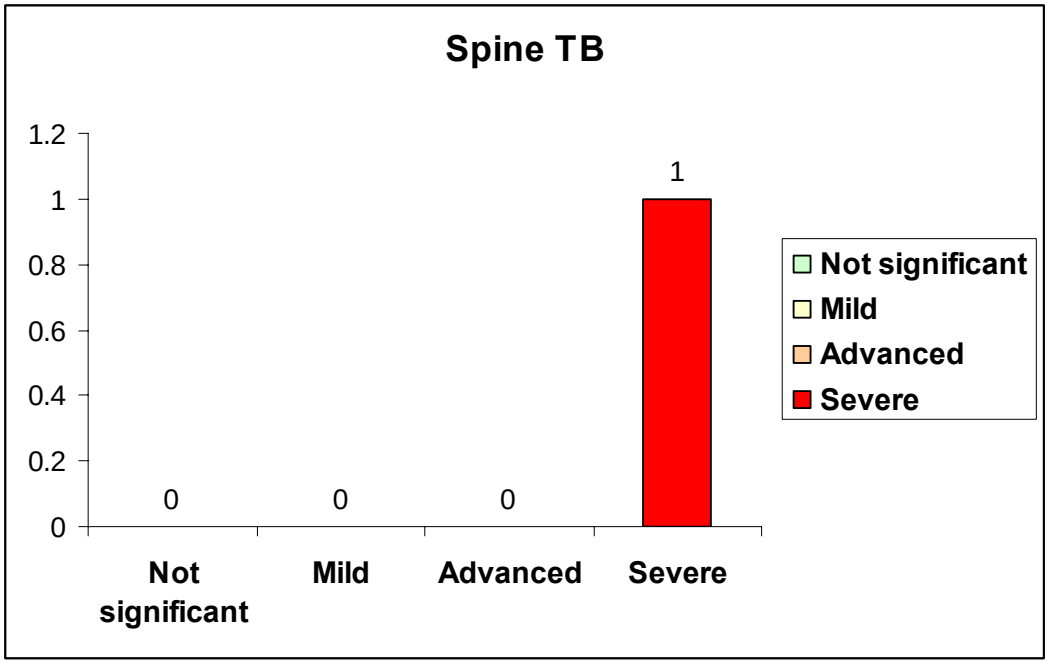
DISTRIBUTION OF CNS TB IN RELATION TO IMMUNOSUPPRESSION



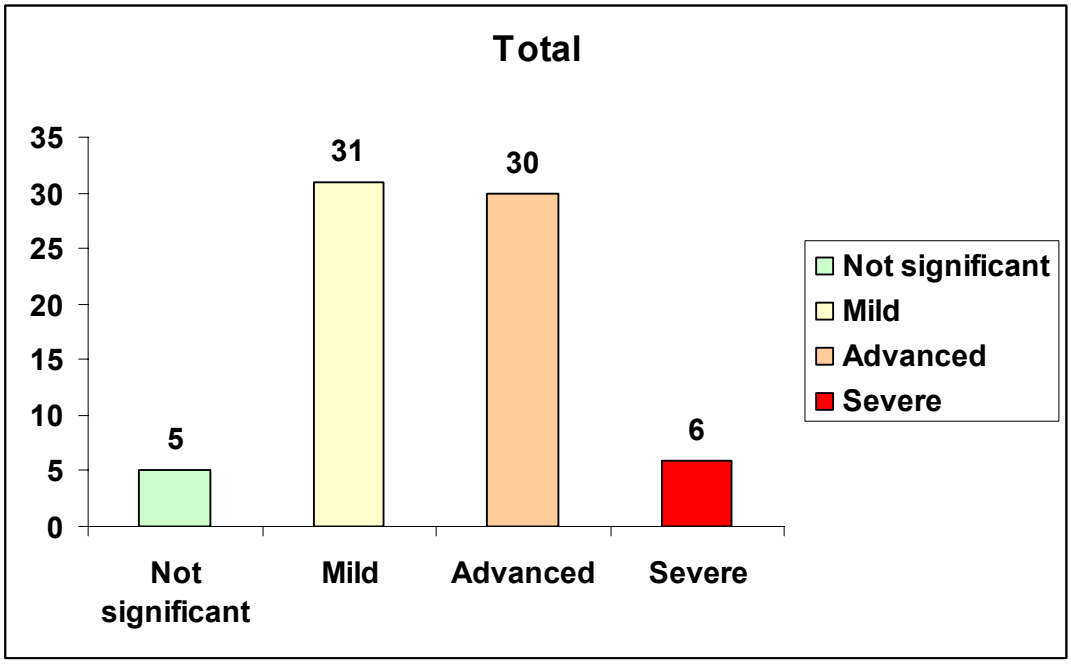
DISTRIBUTION OF ABDOMINAL TB IN RELATION TO IMMUNOSUPPRESSION



DISTRIBUTION OF SPINE TB IN RELATION TO IMMUNOSUPPRESSION



DISTRIBUTION OF TOTAL NO. OF HIV/TB COINFECTED CASES IN RELATION TO IMMUNO SUPPRESSION

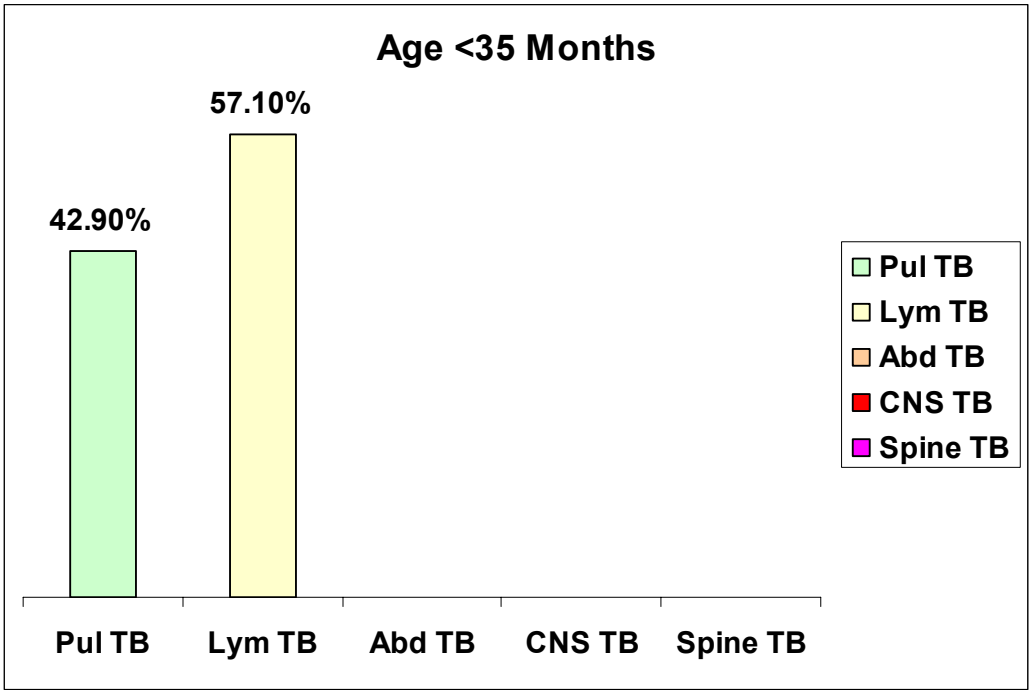


AGE & TUBERCULOSIS TYPE

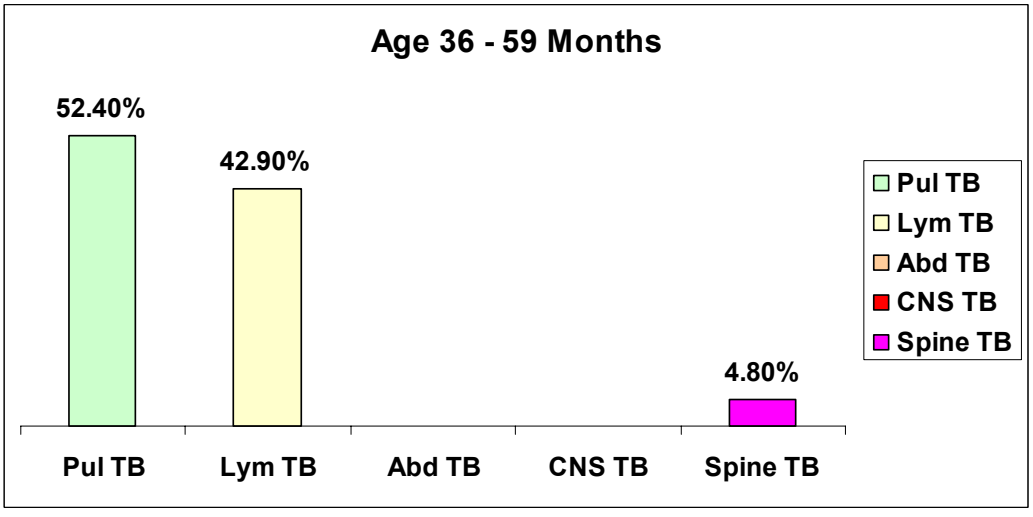
AGE	TB Type					Total
	Pul TB	**Lym TB**	**Abd TB**	**CNS TB**	**Spine TB**	
12 – 35 months No. % of total	3 42.9%	4 57.1%				7 100%
36-59 months No. % of total	11 52.4%	9 42.9%			1 4.8%	21 100%
>60 months No. % of total	30 68.2%	9 20.5%	1 2.3%	4 9.1%		44 100%
Total No. % of total	44 61.1%	22 30.6%	1 1.4%	4 5.6%	1 1.4%	72 100%

In our study, both pulmonary TB as well CNS TB occurred more commonly in children aged more than 60 months of age.

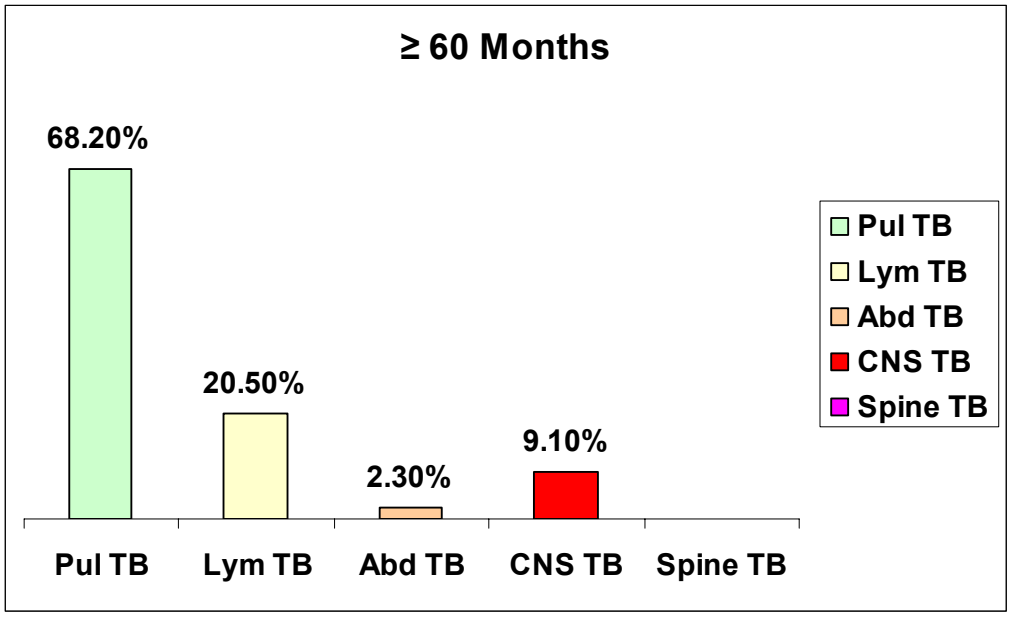
DISTRIBUTION OF TUBERCULOSIS TYPE IN AGE <35 MONTHS



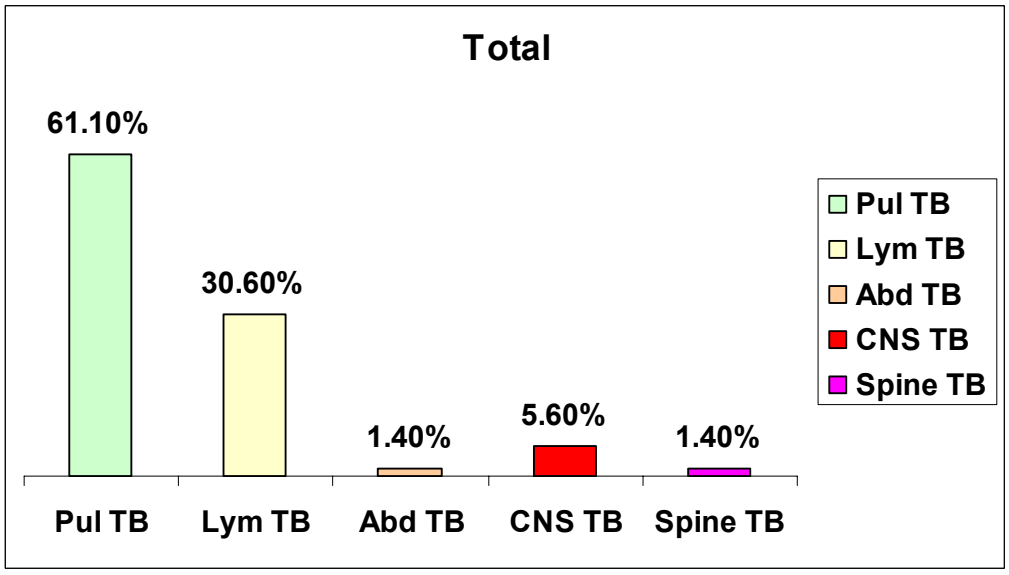
DISTRIBUTION OF TUBERCULOSIS TYPE IN AGE 36 - 59 MONTHS



DISTRIBUTION OF TUBERCULOSIS TYPE IN AGE ≥ 60 MONTHS



AGEWISE DISTRIBUTION OF TOTAL NO. OF HIV/TB COINFECTED CASES WITH TYPES OF TB

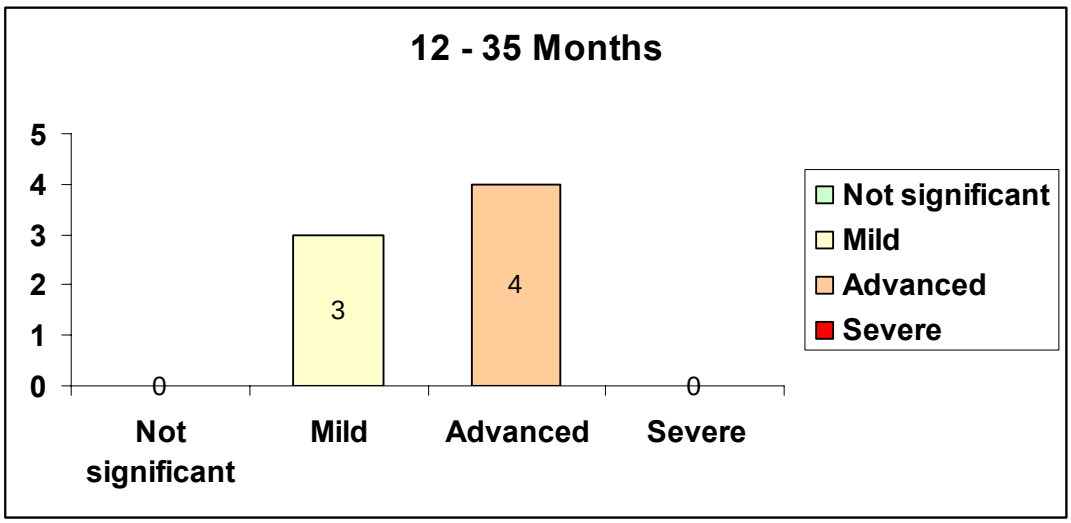


AGE & CD4 LEVEL CORRELATION

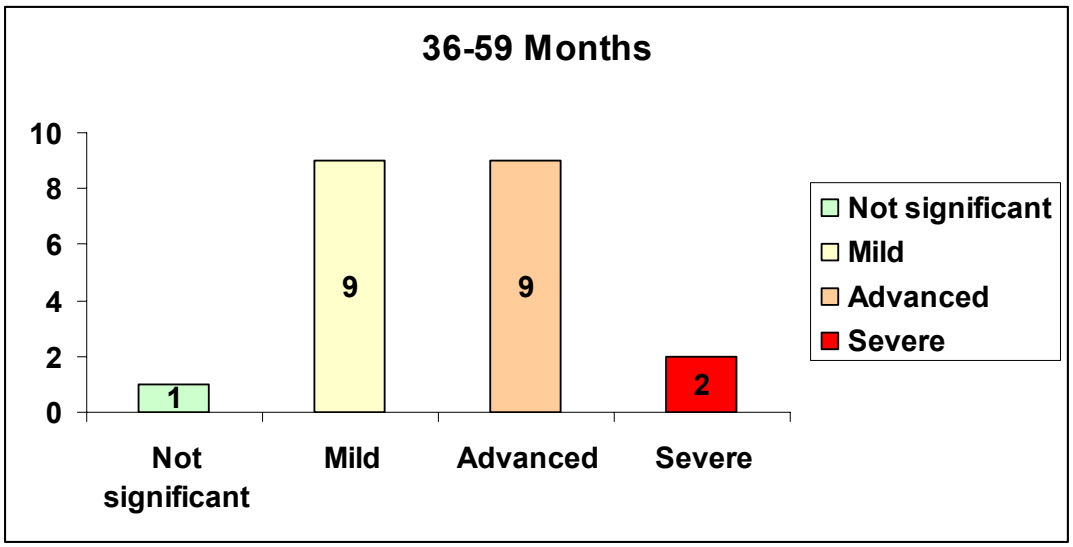
AGE	CD4				Total
	Not significant	Mild	Advanced	Severe	
12-35 months No.		3	4		7
% of total		42.9%	57.1%		100%
36-59 months No.	1	9	9	2	21
% of total	4.8%	42.9%	42.9%	9.5%	100%
>60 months No.	3	22	16	3	44
% of total	6.82%	50.0%	36.36%	6.82%	100%
Total No.	4	34	29	5	72
% of total	5.55%	47.24%	40.27%	6.94%	100%

In our study about 87.58% of HIV-TB coinfected children presented in mild and advanced grade of immuno suppression and about 61.11% of children presented were more than 60 months of age.

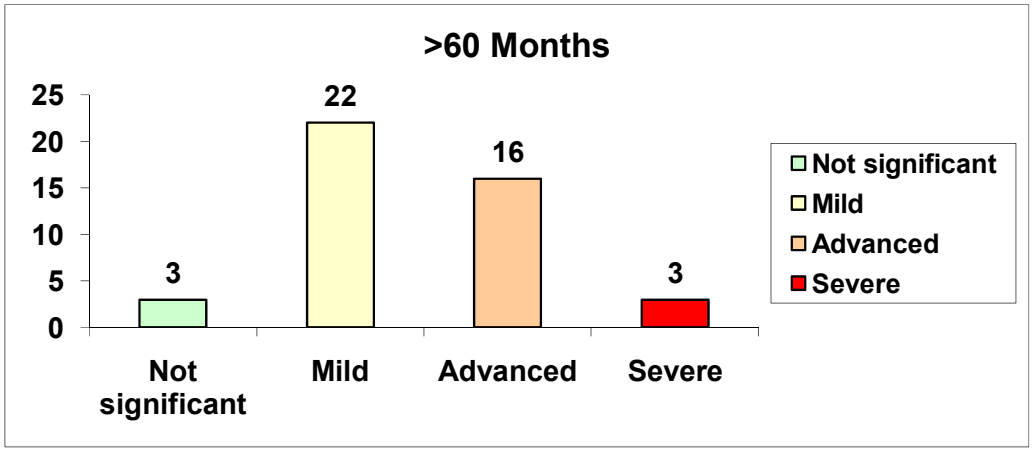
CD 4 COUNT IN 12-35 MONTHS OF HIV / TB COINFECTED CHILDREN



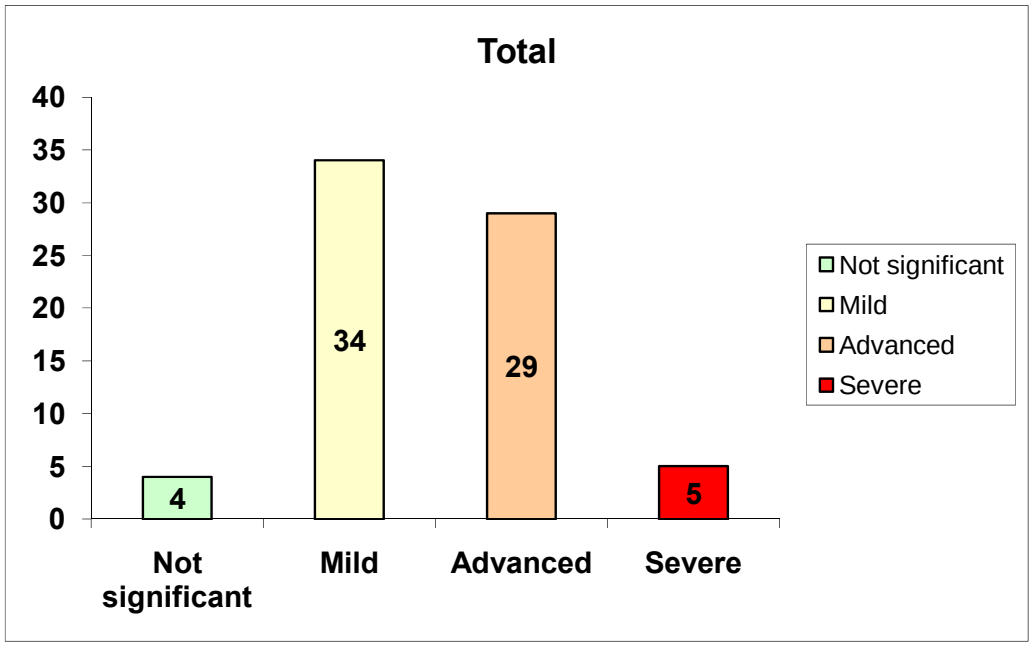
CD 4 COUNT IN 36-59 MONTHS OF HIV / TB COINFECTED CHILDREN



CD 4 COUNT IN >60 MONTHS OF HIV / TB CO INFECTED CHILDREN



AGEWISE DISTRIBUTION OF TOTAL NO. OF HIV/TB COINFECTED CHILDREN WITH CD4 COUNT



DISCUSSION

DISCUSSION

PREVALENCE IN OUR STUDY:

In our study, out of 742 children enrolled from October 2008 to October 2010 in TB clinic in Institute of Child Health and hospital for children, Egmore, Chennai , 72 children were HIV positive .

This implies that 9.7% of tuberculous children were coinfected with HIV which can have a great impact on the morbidity & mortality and treatment outcome of these children.This is very low when compared to studies in South Africa where it was 45%.[21] This is also higher than the 5.12% in an Indian study[22]. This difference could be because of the probable difference in prevalence of HIV in the respective areas.

However this is very similar to the study done in Agra, India [24] which showed a sero prevalence rate of 8.51%.

AGE DISTRIBUTION:

In our study we have classified HIV/TB coinfected children into three groups according to WHO classification. The major chunk was in the age group of more than 5yrs (44%) in our study. This is different from other study[22] which showed an increased prevalence in the age group of 1-5 yrs of age. In the Agra study the highest prevalence was seen in the age group of 2-5 years[24].

SEX DISTRIBUTION:

In our study male children(63.9%) were more affected than female children(36.1%). A similar result was given in the Agra study [24] which showed a high distribution in male (85.61%) than female child (17.39%). This may be due to the parental bias to care more for a male child than a female child in the lower socioeconomic groups who are the major people getting health care in our hospital.

CLINICAL MANIFESTATIONS:

In our study the most common manifestations in HIV/TB coinfected children are fever (100%), cough (88.9%), weight loss(86.1%). History of contact with a known pulmonary TB is seen only in 45.8% of the infected children. Neck swelling is seen in 27% and breathlessness in 21% of children. BCG scar was present only in 36.1% of the coinfected children. Abdominal symptoms were present in 7% and CNS manifestations like seizures and ALOC were seen in 9.8% of patients.

Since pulmonary tuberculosis is the most common type seen in our study, cough was the predominant specific symptom.

TYPES OF TUBERCULOSIS:

In our study pulmonary TB was the most common tuberculosis type(61.1%) followed by lymphatic TB (30.6%). CNS tuberculosis was next (5.6%) and abdominal and spinal TB had a share of 1.4% each.

Overall 39.9% of HIV/TB co infected children had extra pulmonary TB . In the Agra study[24] a similar pattern of distribution with more pulmonary(86.75%) than extra pulmonary TB (13.4%) was found.

CD4 COUNT IN HIV/TB COINFECTED CHILDREN:

In our study 47.2% of the co infected children had mild grade of immunosuppression and 41.7% had advanced grade of immunosuppression.

Only 8.3% of the coinfected children had a CD4 count level which is not significant.

CD4 COUNT CORRELATION WITH TYPES OF TB:

In this study, pulmonary TB is more common in mild grade of immunosuppression(45.5%) than in advanced grade(43.2%) of immuno suppression.

Lymphatic TB is more common in mild grade of immuno suppression(50%) followed by advanced (40.9%) grade of immunosuppression.

CNS (75%) and spinal (100%) TB are present only in severe grade of immuno suppression.

Abdominal TB is seen in advanced grade of immuno suppression.

Similarly pulmonary TB is the most common type in not significant (60%), mild (64.5%) and advanced grade (63.3%) of immunosuppression.

CNS TB is the most common TB (60%) in severe grade of immuno suppression.

The P value is 0.04 and is significant.

AGE AND TUBERCULOSIS TYPE:

In our study in children less than 35 months lymphatic TB is the most common type (57.1%). In children between 36-59 months of age pulmonary TB is more common (52.4%) and in children more than 60 months of age pulmonary TB is the most predominant (68.2%)type.

CNS TB occurred only in children more than 60 months of age (100%).

AGE AND CD4 LEVEL CORRELATION:

In this study 57.1% of children under 35 months had advanced grade of immunosuppression. 86% of children between 36 to 59 months had mild and advanced grade of immuno suppression and 50% of

children more than 60 months of age had mild grade of immuno suppression.

LIMITATIONS OF STUDY

1. The study is done in a tertiary care centre hence the same prevalence need not be true at the community level.
2. This study is done only for a period of 2 years.
3. CD4 count is not done for all tuberculosis patients.
4. Outcome of these HIV/TB co infected individuals was not studied.

CONCLUSION

CONCLUSION

1. The HIV prevalence rate among tuberculous children in our study is 9.7%.
2. Hence screening of all newly diagnosed tuberculous children for HIV coinfection can be undertaken as a routine .
3. Pulmonary TB is the most common type of TB in HIV/TB coinfection in our study.
4. Pulmonary TB is the most common type in not significant , mild and advanced grade of immuno suppression.
5. CNS tuberculosis is the most common type in severe grade of immuno suppression.
6. CNS TB occurred more commonly in children more than 60 months of age.
7. Lymphnode TB is the commonest type of tuberculosis in children with HIV coinfection less than 35 months of age.

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ANNEXURE

ANNEXURE – I

PROFORMA

Name: Age: Sex:

Address: Wt: Height:

S.No	Clinical Features	Yes	No	Duration
1	Fever			
2	Cough			
3	Breathlessness			
4	Weight loss			
5	Chest pain			
6	History of contact with open TB			
7	Neck Swelling			
8	Abdominal Pain			
9	Abdominal Distention			
10	Vomiting / Nausea			
11	Diarrhoea / Constipation			
12	Bleeding per rectum			

13	Jaundice			
14	Bone pain			
15	Visual loss			
16	Seizures			
17	ALOC			
18	Dysuria / Hematuria			
19	Flank pain			
20	BCG			
21	Bony swelling			

Examination:

General Examination:

CVS

Vitals :

Pulse :

Heart Rate:

BP:

RS

P/A

CNS

Lab Investigation:

- Blood:
  - HB
  - TC
  - DC
  - ESR
- LFT
- Urine Microscopy
- Mantoux
- RGJ / Sputum Examination:
- Chest x-ray
- Parentral Screening
- Biopsy / FNAC
- USG Abdomen
- Barium Meal / Enema
- Bronchoscopy: BAL for Bactec,
- Quantiferon Assay
- CT Chest
  - Brain
  - Abdomen
- ELISA
- PCR ASSAY
- CD4 Cell Count